Amendments to the Specification

Please replace paragraph on page 4, line 1, with the following amended paragraph:

In sinus arrhythmia there are cyclic changes in the heart rate during breathing. In sinus tachycardia the sinus node sends out electrical signals faster than usual, speeding up the heart rate. In sick sinus syndrome the sinus node does not fire its signals properly, so that the heart rate slows down. Sometimes the rate changes back and forth between a slow (bradycardia) and fast (tachycardia) rate. With premature supraventricular contractions or premature atrial contractions (PAC) a heartbeat occurs early in the atria, causing the heart to beat before the next regular heartbeat. In supraventricular tachycardia (SVT) and paroxysmal atrial tachycardia (PAT) a series of early beats in the atria speed up the heart rate (the number of times a heart beats per minute). In paroxysmal tachycardia repeated periods of very fast heartbeats begin and end suddenly. In [[in]] atrial flutter there are rapidly fired signals which cause the heart muscles in the atria to contract quickly, leading to a very fast, steady heartbeat. In atrial fibrillation electrical signals in the atria are fired in a very fast and uncontrolled manner. The electrical signals arrive in the ventricles in a completely irregular fashion, so the heartbeat is completely irregular. In the Wolff-Parkinson-White syndrome[[.]], abnormal pathways between the atria and ventricles cause the electrical signal to arrive at the ventricles too soon and to be transmitted back into the atria. Thus very fast heart rates may develop as the electrical signal ricochets between the atria and ventricles.

Please replace paragraph on page 10, line 1, with the following amended paragraph:

Ablation of the slow AV nodal pathway is the same procedure used to treat AV nodal reentrant tachycardia. For uncontrollable atrial fibrillation and other supraventricular tachycardias, this procedure offers some of the benefit of AV junctional ablation without the need for implantation of a permanent pacemaker. The slow AV nodal pathway procedure takes advantage of the fact that ~~the following:~~ the heart in most patients has two parts to the AV node. The "fast" AV nodal pathway conducts rapidly but takes a long time to recover enough to conduct the next heartbeat. The "slow" AV nodal pathway is a backup pathway that conducts slowly but can recover very quickly. At most heart rates, patients use only the fast pathway. When the heart is beating very rapidly (during vigorous exercise, for example), the slow pathway is used because the fast pathway can't recover fast enough between heartbeats. When the slow pathway is removed by ablation, the patient almost never can tell the difference at usual heart rates (even during vigorous exercise to, say, a heart rate of 180-200 beats per minute). If a very rapid heart rate (say, to 250 bpm) occurs in the atria, however, the ventricles will go more slowly than they would with an intact slow pathway.

Please replace paragraph on page 10, line 20, with the following amended paragraph:

In older patients, who are the ones who usually develop sustained atrial fibrillation, the fast pathway does not conduct as rapidly as in young people, so the maximum heart rate can often be reduced to a range that is tolerable. Two problems with the slow AV nodal procedure for atria fibrillation are, first, when the procedure is continued until the heart rate in atrial fibrillation is reasonable (say, 130 bpm during infusion of

isoproterenol, which speeds up the heart rate), about 20% of patients get complete heart block and require immediate implantation of a permanent pacemaker. Second, patients who have undergone the slow AV nodal procedure often don't feel as well as those who go ahead and have AV junctional ablation and pacemaker insertion. The reason seems to be that the heart rate is still erratic because the ventricular rhythm still follows the irregularly ~~irregular~~ atrial fibrillation. By contrast, patients who have AV junctional ablation and pacemakers have regular rhythms because the pacemakers set the heart rate for them.

Please replace paragraph on page 11, line 13, with the following amended paragraph:

Finally, arrhythmia can also be treated by implantation of a cardiac defibrillator or by implantation of an artificial pacemaker. A cardiac defibrillator is surgically implanted beneath the skin of a patient's abdomen and connected by wires to the ventricles. When arrhythmia occurs, the defibrillator sends an electrical charge to the heart in an attempt to restore normal heartbeat. A defibrillator does not prevent the onset of arrhythmia, but merely attempts to restore the heart's normal rhythm by providing an electric shock to the heart to disrupt an ongoing arrhythmia. Importantly, both defibrillators and pacemakers can malfunction and misfire due, for example, to the effect of proximity to an airport metal detector or store security check out device. Furthermore, significant drawback to [[with]] the use of both defibrillators and pacemakers include the requirement for surgery to implant with attendant risks such as infection.

Please replace paragraph on page 11, line 27, with the following amended paragraph:

A commonly prescribed drug for angina is nitroglycerin, which relieves pain by widening blood vessels. More blood can thereby [[to]] flow to the heart muscle and the workload of the heart is decreased. Nitroglycerin can be administered when discomfort occurs or is expected. Other drugs to treat angina include beta blockers to slow the heart rate and lessen the force of the heart muscle contraction and calcium channel blockers for reducing the frequency and severity of angina attacks.

Please replace paragraph on page 16, line 4, with the following amended paragraph:

Botulinum serotypes B, C1, E and F demonstrate a lower potency [[that]] than BOTOX® and would therefore [[by]] be used in greater amounts.

Please replace paragraph on page 20, line 17, with the following amended paragraph:

Another preferred method within the scope of the present invention can be carried out by locally administering the neurotoxin to a cardiac muscle to treat the cardiac muscle disorder. Local administration of the neurotoxin to the desired cardiac muscle can be carried out by ~~intrapericardially~~ intrapericardial injection or infusion of the neurotoxin, by therapeutic cardiac catheterization or by direct intracardiac muscle injection of the neurotoxin.

Please replace paragraph on page 23, line 10, with the following amended paragraph:

Thus, when atropine is ineffective and the patient has symptomatic bradycardia, vagal nerve inhibition and hence an increase in heart rate can be accomplished by administration of botulinum toxin to the heart [[to]], as for example in the vicinity of the SA node. Botulinum toxin administration can be accomplished by direct local injection to cardiac muscle, by cardiac catheterization or by intrapericardial injection or infusion. Significantly, a single administration injection of the botulinum toxin substantially reduces the symptoms of the bradycardia for from about two to about four months.

Please replace paragraph on page 25, line 7, with the following amended paragraph:

The specific dosage appropriate for administration is readily determined by one of ordinary skill in the art according to the factor discussed above. Additionally, the estimates for appropriate dosages in humans can be extrapolated from determinations of the amounts of botulinum required for effective denervation of other non-cardiac muscles. Thus, the amount of botulinum A to be injected is proportional to the mass of the cardiac muscle to be denervated. Generally, between about 0.01 and 30 units of a botulinum toxin per kg of total patient weight can be administered to effectively accomplish a toxin induced reversible postganglionic vagectomy upon administration of the neurotoxin at or to the vicinity of arrhythmic cardiac tissue. Less than about 0.01 U/kg of a botulinum toxin does not have a significant therapeutic effect, while more than about 30 U/kg of a botulinum toxin [[can]] approaches the safety margin for a toxic dose. In exigent circumstances, up to about 35 U/kg of a botulinum toxin can be administered by local administration. Careful placement of the injection needle and a low volume of neurotoxin used prevents significant amounts of botulinum toxin

from appearing systemically. A more preferred dose range is from about 0.1 U/kg to about 25 U/kg of a botulinum toxin. A most preferred dose range is from about 1 U/kg to about 20 U/kg of BOTOX®. The actual amount of U/kg of a botulinum toxin to be administered depends upon factors such as the extent (mass) of the arrhythmic tissue to be treated and the administration route chosen (i.e. by cardiac catheterization or by intrapericardial administration). Botulinum toxin type A is a preferred botulinum toxin serotype for use in the methods of the present invention.

Please replace paragraph on page 26, line 21, with the following amended paragraph:

Local, intracardiac catheter mediated delivery of a neurotoxin can be accomplished by use of a microporous infusion catheter (see e. g. Am Heart J. 1996 Nov;132(5):969-72 and Cath & Cardiovasc Diagn 1997 Nov;42(3):313-20) suitably modified to infuse the neurotoxin directly into the adjacent cardiac tissue at a relatively high pressure with minimal injury to the cardiac tissue. Other mechanisms for local[[.]] intracardiac neurotoxin delivery include eluting stents, microspheres, neurotoxin-coated hydrogel (which can absorb hydrophilic drugs, such as botulinum toxin) balloon, iontophoretic devices and endocardiac paving and adhesive ~~devises~~ devices. The later method is carried out by catheter assisted lodging of a neurotoxin containing adhesive at or near a site of arrhythmic cardiac tissue (see e.g. Int J Artificial Organs 1997 Jun;20(6):319-26).

Please replace paragraph on page 27, line 4, with the following amended paragraph:

Furthermore, the present invention also includes within its scope local administration of a neurotoxin to cardiac muscle by

controlled release implants which are placed in direct contact with the pericardium, the epicardium or placed intracardially by catheterization. The neurotoxin is imbedded into or absorbed by the implant material prior to placement of the implant on or adjacent to a site of a cardiac muscle to be treated for a cardiac muscle disorder. Thus, the controlled release materials and procedure as set forth in J Cardio Pharm 24:826-840 (1994) (the contents of which publication are incorporated herein in its entirety), can be adapted by one of ordinary skill in the art for local administration of a neurotoxin according to [[ht]] the present invention.

Please replace paragraph on page 28, line 6, with the following amended paragraph:

Botulinum toxin can also be used as a prophylactic agent to treat post operative atrial fibrillation. To treat post operative arrhythmia, the botulinum toxin is ~~local~~ locally administered 5-20 days before the surgery and again after surgery. The benefits of prophylactic therapy can include significant reductions in morbidity, hospital length of stay and overall costs. Botulinum toxin can also be used to treat angina.

Please replace paragraph on page 29, line 7, with the following amended paragraph:

(a) Direct, injection of botulinum toxin to cardiac muscle can be carried out by an endomyocardial procedure where the biotome is replaced by a hollow needle through which a bolus injection of the toxin can be accomplished. Right ventricular injection can be accomplished by introducing a No. 7-9F catheter with a retractable sheathed needle via the right internal jugular vein using the usual Seldinger technique. The catheter is

advanced under fluoroscopic guidance to the lateral wall of the right atrium. Using counterclockwise rotation, the catheter is advanced across the tricuspid valve and toward the interventricular septum. Position of the catheter against the interventricular septum is confirmed using 30 degrees right anterior oblique and 60 degree left anterior oblique fluoroscopic projections. Alternately, two dimensional echocardiography can be used to guide the position of the catheter. Contact with the myocardium is confirmed by the presence of premature ventricular contractions, lack of further advancement and transmission of ventricular impulse to the operator. The catheter sheath is then withdrawn to expose the needle tip. The catheter is readvanced to contact the myocardium and embed the needle therein. Secure lodgment of the needle tip within the myocardial wall is confirmed by fluoroscopy and [[be]] by resistance to an operator applied slight withdrawal pressure (tugging) upon the catheter. 0.3 U/kg to 5 U/kg of BOTOX® are then injected into the myocardium and the catheter withdrawn. Right or left ventricular injection can also be accomplished from the femoral vein. The specific amount of BOTOX® administered by this intracardiac procedure depends upon a variety of factors to be weighed and considered within the discretion of the attending physician.

Please replace paragraph on page 30, line 1, with the following amended paragraph:

At the determined, localized site of arrhythmic cardiac tissue, botulinum toxin type A (available from Allergan, Inc., of Irvine, California under the trade name BOTOX®) can be injected into the cardiac muscle through a 4 mm sclerotherapy needle passed through the infusion channel of the catheter and connected to a gravity driven device (overhead) or pump for infusion of the BOTOX® into the selected cardiac tissue.

Please replace paragraph on page 30, line 24, with the following amended paragraph:

Subsequent to BOTOX®, neurotoxin efficacy can be evaluated by the same means [[use]] used to evaluate the effect of anti-arrhythmic drugs, such as by electrocardiogram (ECG).

Please replace paragraph beginning on page 30, line 28, with the following amended paragraph:

Within seven days the bradycardia symptoms have substantially diminished and remain significantly alleviated for two to four months post injection. Insignificant amounts of the botulinum toxin [[enter]] appear systemically with no significant side effects.

Please replace paragraph beginning on page 31, line 19, with the following amended paragraph:

(b) An alternative intrapericardial procedure for local cardiac drug delivery without system drug effect can also be accomplished by accessing the normal pericardial space through the right atrial appendage. The transatrial technique for accessing the pericardial space is as follows. An 8-F multipurpose guide is positioned under fluoroscopic guidance in the right atrial appendage. A custom fabricated 4-F catheter with a 21 gauge needle mounted at the tip is advanced through the guide, and a small perforation is made in the right atrial appendage. A soft 0.014 inch (0.036 cm) guide wire is advanced through the needle catheter and into the normal pericardial space. The guide [[wore]] wire confirms position in the

pericardial space by conforming to the contour of the heart, secures the point of entry and allows over the wire exchanges of other catheters. The needle catheter is withdrawn over the wire and exchanged for a 4-F catheter with multiple side holes at its distal end, which is positioned and left in the pericardial space for delivery of neurotoxin. Radiopaque markers at the tip of all catheters improve visualization during fluoroscopy. Intrapericardial BOTOX® 0.3 U/kg to 5 U/kg is injected through the 4-F intrapericardial catheter without rapid diffusion into the systemic circulation.